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Transthyretin – An Explanation of "Anomalous" Serum Thyroid Hormone Values in Severe Illness?

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Summary: The following serum analytes were measured in 464 patients with defined carcinomas and other tumours as well as those with chronic obstructive lung disease and under regular haemodialysis, and in 261 healthy controls: thyrotropin (TSH), thyroxine (T_4), triiodothyronine (T_3), free thyroxine (fT_4), thyroxine binding globulin (TBG) and transthyretin (TTR).

The following ratios were constructed:
$fT_4 \times$ TTR, defined as the thyroxine availability index
fT_4/TTR, defined as the thyroid hormone compensation index
$100 \times T_3$/TBG as the free T_3 index (fT_3I) and
$fT_3I \times$ TTR, defined as the triiodothyronine availability index.

Significantly elevated thyrotropin values ($p = 0.05$) were only found in patients with breast cancer when compared with age matched controls, although elevated T_4 and fT_4 values were found in all experimental groups except the haemodialysis patients ($p < 0.01$). The thyroxine availability index and triiodothyronine availability index values were not significantly different from the age matched controls (> 60 a) in the cancer groups, showing that the transthyretin concentrations compensated for changes in fT_4 or vice versa. These findings are reflected in the euthyroid thyrotropin values. The T_4 and fT_4 values in the dialysis patient group were significantly lower than in the age matched controls ($p < 0.01$), while the transthyretin values were significantly higher ($p < 0.01$), which accounted for the normal thyroxine availability index and euthyroid thyrotropin values.

Introduction

Despite the fact that transthyretin (TTR) has been known for many years to transport thyroid hormones (1) it has never been used as a routine thyroid function parameter.

Interest has been shown in its association with nutritional states, especially in patients under intensive care (2–4) and with cancer (5). The main interest in transthyretin in recent years has been in its association with familial amyloidosis (6, 7).

Abdukarimov (8) showed that transthyretin is able to permeate the cell membrane and transport thyroid hormones into the cell, a property which would make transthyretin an active partner in thyroid hormone availability.

Newer investigations of the actions of thyroid hormones at the cellular level by *Oppenheimer* et al. (9) have also mentioned a receptor of $M_r = 50\,500$ and a protein of $M_r = 56\,000$ in the nucleus, both of which bind T_3. Although the relative molecular mass of both proteins was similar to that reported for transthyretin $M_r = 55\,000$ (10), there is no evidence to connect transthyretin with these proteins which are structurally dissimilar (11, 12).

There are many diseased states where thyrotropin concentrations are normal, but where other thyroid parameters are pathological.

The aim of this article was to investigate the role of transthyretin in chronically sick patients and how it relates to conventional thyroid hormone parameters such as thyrotropin, thyroxine binding globulin (TBG), T_4, T_3 and fT_4.

As there are three possible mechanisms by which T_3 and T_4 can enter the cell (receptor-mediation, diffusion as fT_4 and fT_3 or, if *Abdukarimov* is correct, coupled to transthyretin (TTR)), the following quotients were constructed:

a. $fT_4 \times$ TTR – defined as the thyroxine availability index

b. fT_4/TTR – defined as the thyroxine compensation index

c. $fT_3I \times$ TTR – defined as the triiodothyronine availability index

The thyroxine availability index and to a lesser extent, the triiodothyronine availability index represent the potential transport capacity of thyroid hormones into the cell via the two routes described above.

The thyroxine compensation index reflects the inverse behaviour of both transport systems.

A triiodothyronine compensation index was not calculated, as the peripheral conversion of T_4 to T_3 occurs mainly in the cell via the 5′-deiodinase (13). Human liver is also a potent source of 5′-deiodinase, but reverse triiodothyronine (rT_3) is the preferred substrate (14).

In addition, the T_3/TBG quotient was used to calculate an fT_3 index (fT_3I). A total of 725 individuals was studied over a three-year period, the main results of which are summarised in this publication.

Materials and Methods

Control groups

As the concentration of many thyroid parameters in blood is age-dependent, the concentrations of analytes were also measured in three control groups with normal thyroid function.

Persons taking oral contraceptives were excluded, as were those with positive antibody titers to microsomal peroxidase and thyroglobulin. All persons were healthy in terms of subjective wellbeing, and had normal aminotransferase, γ-glutamyltransferase, serum creatinine and blood smear.

Group 1 consisted of adults under 40 (n = 115),
group 2 of persons between 40 and 60 (n = 116) and
group 3 of persons over 60 years of age (n = 30).

The "over-60" group was used as an aged-matched control for the sick groups, as the age ranges of these groups did not differ significantly. The reason for the 3 control groups was to confirm that the analyte concentrations found in normal euthyroid persons were comparable with those already published by other workers.

As the results from the two younger control groups were not used for further comparison, sex-linked hormone differences in women of child-bearing age were not taken into account.

The "over-60" group consisted of active individuals in a rural area, who were healthy except for a few cases of partial deafness.

Experimental groups

These consisted of defined cancer patients, which were grouped as follows:

Various carcinomata (n = 59),
other malignant tumour-bearers without carcinomata (n = 43),
breast cancer (n = 45),
gastrointestinal cancer (n = 63),
lung cancer (n = 50) and
ovarian cancer (n = 43).

The group of patients with various carcinomata included cases of cancer of the cervix, uterus, vagina, head and neck, oesophagus, gall bladder, pancreas and a primary hepatoma. The tumour group consisted of patients with lymphoma, *Hodgkin*'s disease, leukaemia (acute lymphatic (ALL), acute myeloic (AML), chronic lymphatic (CLL), chronic myeloic (CML)), melanoma, sarcoma and teratoma. Fifty three patients with chronic obstructive lung disease who had no malignant disease were included in the study, as were 58 patients under haemodialysis, as these groups represented patients with metabolic and respiratory acidosis and dysproteinaemia.

In addition, 58 patients suffering from hypo- and hyperthyroidism, who attended to thyroid outpatient clinic, were examined either before, or during treatment, the criterion for inclusion in this study being an abnormal thyrotropin value on the first admission to the outpatient clinic. These patients were examined in the initial phase of treatment – i.e. before the thyrotropin concentrations returned to normal.

Methods

The following methods were used to determine the concentrations of the parameters measured in this study.

In-house immunoluminometric assays were used to measure thyrotropin, thyroxine binding globulin and transthyretin, and they have been published in detail elsewhere (15–17). T_3 was measured with a luminescence enhanced enzyme immunoassay (Amerlite–Amersham-Buchler, Braunschweig, FRG.).

T_4 and fT_4 were measured with the SPAC-ET radioimmunoassay (Byk-Sangtec, Dietzenbach, FRG.) using an indirect calculation (two-tube method) for the estimation of free thyroxine.

Statistics

Non-parametric statistics were used throughout as the data were not normally distributed. The *Mann-Whitney* U-test with z-transformation was used for independent data pairs. Median values and relevant percentiles are used throughout. Significance levels were given at the 5% and 1% levels ($p \leqslant 0.05$ or 0.01). For testing the variances of the three reference collectives, the *Kruskal-Wallis* test was applied.

Tab. 1. Laboratory internal reference ranges for the parameters measured in this publication. All values are for adults not undergoing oral contraceptive or oestrogen treatment.

Component	Hypo-thyroid	Euthyroid	Hyper-thyroid
Thyrotropin (mU/l)	> 5.00	0.25 – 3.50	< 0.20
Thyroxine binding globulin (mg/l)		12 – 31	
T_4 (nmol/l)	<40	50 – 150	>160
T_3 (nmol/l)	< 1.00	1.15 – 2.55	> 2.75
Transthyretin (g/l)		0.10 – 0.45	
fT_4 (pmol/l)	< 8	10 – 28	> 35
		Normal Range	
$fT_4 \times TTR^1$		1.25 – 6.25	
fT_4/TTR^2		25 – 130	
$fT_3I \times TTR^3$		0.30 – 3.20	
$100 \times T_3/TBG^4$		7.5 – 9.5	

Key: 1 – Thyroxine availability index
2 – Thyroxine compensation index
3 – Triiodothyronine availability index
4 – Free triiodothyronine index
These abbreviations are used in the subsequent tables

Tab. 2. Median values for the control groups together with significance levels, where relevant.

Parameter	Group 1 <40a	Group 2 40–60a	Group 3 >60a
Thyrotropin (mU/l)	1.20	1.00	1.01
fT_4 (pmol/l)	12.8*	11.6	12.0
Transthyretin (g/l)	0.23	0.23	0.18*
Thyroxine binding globulin (mg/l)	21*	19	16*/+
T_4 (nmol/l)	98*	85	87+
T_3 (nmol/l)	1.77*	1.51	1.48
fT_4/TTR	56	50	67
$fT_4 \times TTR$	2.94	2.67	2.16
$fT_3I \times TTR$	1.25	1.25	1.16
$100 \times T_3/TBG$	8.4	8.0	9.2*

Significant differences ($p < 0.05$):
+ from group 1
* from group 2

Results

Reference group values

Table 1 shows the laboratory internal reference ranges for healthy individuals for the parameters measured. These are for adults aged 18–65 and have been established over long periods for the methods described here.

Table 2 shows the median values of the measured parameters in the three control groups, as well as the values for the constructed quotients. The median ages of the groups were 24, 46 and 63 years respectively.

Experimental group values

Table 3 shows the distribution of results for the different groups. The median ages of the groups lay between 59 and 69 years. Figures 1a–1f show the data from the 58 hyper- and hypothyroid patients and show especially the interesting behaviour of the thyroxine availability index in the treated hypothyroid patients. The data is presented visually in the form of box and whisker diagrams (18). In hyperthyroid patients, the fT_4, triiodothyronine and thyroxine availability indices decreased significantly ($p \leqslant 0.01$) during treatment. Hypothyroid patients showed significant increases in the fT_4, fT_3I, transthyretin, thyroxine and triiodothyronine availability indices. Thyrotropin concentrations in the hyperthyroid groups were all non-detectable (≤ 0.03 mU/l). Median thyrotropin levels were 35 mU/l in the untreated hypothyroid patients, and 18 mU/l under treatment.

Thyrotropin values were significantly higher in the breast cancer group, which agrees with published data (19). Many of the women in this group were under hormone therapy, the nature of which was dependent upon whether the tumour was oestrogen receptor-positive or not. Individual therapy was not controlled, as this was not part of the study.

Tab. 3. Distribution of results in the experimental groups, together with age ranges.

Parameter	Various carcinomata	Tumour (but no carcinomata)	Breast cancer	Gastro-intestinal cancer	Lung cancer	Ovarial cancer	Chronic obstructive lung disease (no malignancy)	Haemodialysis
Thyrotropin (mU/l)	1.09	1.21	1.24	1.04	0.98	0.62	1.10	1.30
fT_4 (pmol/l)	15.0	15.4	14.4	14.9	13.7	14.8	14.1	8.61
Transthyretin (g/l)	0.16	0.17	0.16	0.15	0.15	0.21	0.22	0.40
Thyroxine binding globulin (mg/l)	23	22	26	22	22	24	19	13
T_4 (nmol/l)	100	104	103	107	98	114	107	74
T_3 (nmol/l)	1.91	1.71	1.91	1.92	1.98	2.13	1.92	1.30
fT_4/TTR	94	91	90	99	91	70	64	30
$fT_4 \times TTR$	2.40	2.62	2.30	2.24	2.06	3.11	3.10	2.50
$fT_3I \times TTR$	0.90	0.92	0.80	0.78	0.66	1.14	1.28	1.67
$100 \times T_3/TBG$	8.3	7.7	7.3	8.7	9.0	8.9	10.1	10.0

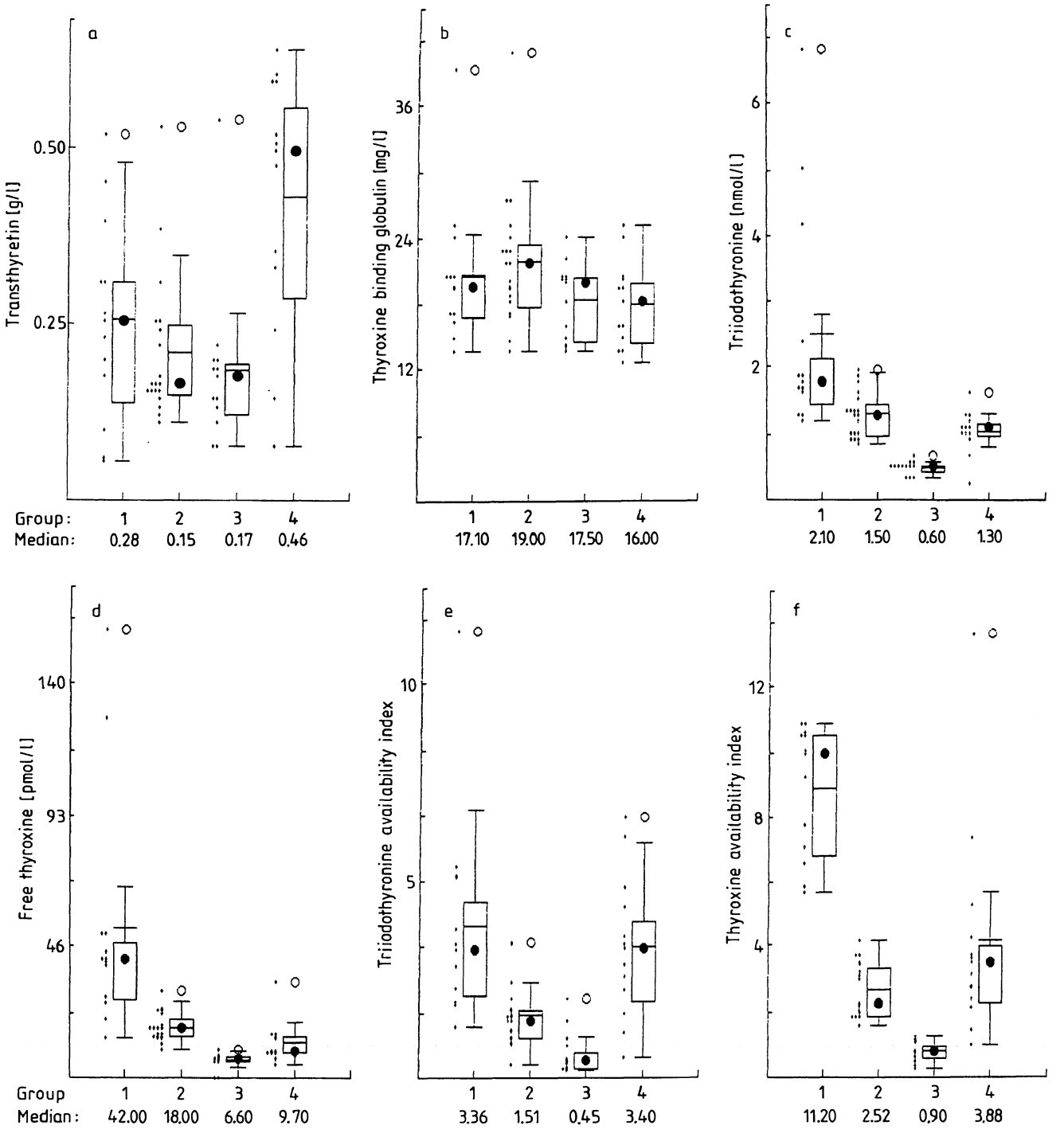
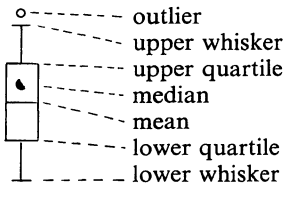


Fig. 1a–1f. Box and whisker diagrams for the distribution of the data from 58 untreated and treated hyper- and hypothyroid patients with abnormal serum thyrotropin values.

1. hyperthyroid patients – untreated (n = 13)
2. hyperthyroid patients – under treatment (n = 19)
3. hypothyroid patients – untreated (n = 13)
4. hypothyroid patients – under treatment (n = 13)

Individual values are shown beside each box and whisker diagram. The median values for each group are shown in the upper right hand corner of each figure.



FT_4 was significantly higher in all cancer groups and in the chronic obstructive lung disease group. It was significantly lower in the dialysis patients.

Transthyretin concentrations were significantly lower in the breast cancer and lung cancer groups. They were significantly higher in the dialysis patients.

Thyroxine binding globulin and T_4 levels were significantly higher in all groups except the dialysis patients, where significantly lower values were found.

T_3 levels were significantly higher in all groups except the chronic obstructive lung disease patients, where they were significantly lower. The free triiodothyronine index (fT_3I) was significantly lower in the tumour groups.

The triiodothyronine availability index values were significantly lower in the tumour, gastrointestinal, breast and lung cancer groups, and significantly higher in the dialysis patients.

The triiodothyronine availability index behaved differently from the thyroxine availability index, which may be associated with the peripheral deiodination of T_4.

The thyroxine compensation index was significantly higher in all the cancer groups, and it was significantly lower in the dialysis group. The thyroxine availability index was not significantly different from the "over-60" control group. In the control groups there was no significant correlation between the transthyretin and fT_4 values, which shows the independence of both thyroid hormone transport pathways under healthy conditions.

Discussion

Thyroid status in chronic disease and cases of dysproteinaemia has been discussed for over two decades. Critical observations have been made on hyperthyroidism in elderly chronically ill patients, and large fluctuations in thyroid hormone levels in individual patients have been reported (20). The question has been raised as to whether secondary hypothyroidism is present in severe non-thyroidal illness, in view of a blunted thyrotropin response and low T_4 levels in severely ill patients (21).

In a comprehensive review on the "euthyroid sick syndrome" *Wartofsky & Burman* (22) came to the conclusion that despite abnormal single thyroid hormone parameters, most sick patients without manifest thyroid disease were euthyroid, based on the serum thyrotropin value as the indicator of thyroid status.

An increased incidence of low T_3 levels in lung cancer cases has been described (23) as well as increased thyrotropin levels in lymphoma patients undergoing radiation treatment (24), although this could not be confirmed in the tumour group in the present study which also contained such patients.

The lower thyroid hormone levels in patients with chronic renal failure is well documented (25) and these findings are augmented by the findings of the present study. The variation of transthyretin levels in disease is less well known; *Kirby* et al. (26) reported that transthyretin synthesis is reduced during "surgery of moderate severity" and that this had an effect on thyroid function in such patients.

The rise in transthyretin values under nutritional therapy has been published for undernourished neonates and infants (3, 4), as well as in chronically ill patients (2), where transthyretin and retinol binding protein were the best indices of malnutrition.

The fall in transthyretin and thyroxine binding globulin in elderly people, even when these lead an active life, as was the case of the "over-60" control group, may reflect a lowering of the metabolic rate combined with a nutritional component. This is supported by the fall in the thyroxine availability index in healthy individuals with increasing age. Perhaps this is related to the process of aging itself or it may be the result of other factors. If the serum thyrotropin level is taken as the index of thyroid status, then 33 of the 423 patients in the experimental groups (excluding the 58 patients with known hyper- and hypothyroidism) had a level of under 0.2 mU/l and could be described as primary hyperthyroid or secondary hypothyroid. Three patients had a thyrotropin of above 5 mU/l and could be classed as primary hypothyroid or secondary hyperthyroid. In terms of percentages the figures are 7.8% and 0.71% for low and high thyrotropin respectively, and they agree with the frequency found in other reports (22).

The thyroxine availability index allows the potential thyroid hormone availability at the cellular level to be determined. In dysproteinaemia, which is found in the majority of dialysis patients, the high circulating transthyreotin levels are compensated for by a reduction of the free thyroid hormone concentrations, as shown in table 3. The triiodothyronine availability index did not appear to play as important a role as the thyroxine availability index, although intracellular deiodination of T_4 to T_3 may "bypass" any effect seen in this index.

Similarly, in cases of reduced transthyretin concentrations, as is often the case in chronic illness, the free

thyroid hormone fraction is elevated, as reflected in the thyroxine compensation index. The importance of transthyretin can be seen in the hyper- and hypothyroid patient groups. Where excessively high free thyroid hormones were measured it was often seen that the transthyretin levels were reduced to subnormal values, although this was not always the case. In contrast, the treatment of overt hypothyroid patients with thyroxine led to an increase in transthyretin synthesis (fig. 1a) in the phase where pituitary regulation was still abnormal (thyrotropin still elevated, despite normalised thyroid hormone values). this may be explained as a response at the cellular level to maximise the inflow of available thyroid hormones in the phase of increased energy demand. Figure 1 supports the claim that the thyroxine availability index reflects thyroid status (figs. 1a, 1d) and can be used in monitoring the efficacy of thyroid treatment (figs. 1e, 1f). Similar findings have been described by *Ishida* et al. (27), who noticed that transthyretin levels did not return to normal in treated hypo- and hyperthyroid patients until a euthyroid state was attained.

It must be born in mind that transthyretin not only transports thyroid hormones, but also other hormones and substances such as thymulin (28) and vitamin A in complex with retinol binding protein (11). Transthyretin may serve as a detoxification mechanism for dioxins (29) and beryllium (30). The multifunction of transthyretin must be taken into account when trying to complete the picture in cases of transthyretin deficiency.

To summarise, the value of transthyretin in helping to explain thyroid function at a cellular level has been demonstrated, especially when combined with the free thyroid hormone levels. The thyroxine availability index reflects the metabolic capacity at cellular levels, and should be included as part of a routine investigation of thyroid status in chronic illness.

The expected thyrotropin response is seen only when the thyroxine availability index moves out of the euthyroid range. In the present study, this was not the case in the cancer and dialysis groups, as the thyroxine availability index, despite abnormal fT_4 values in certain groups, was normal due to compensatory transthyretin concentration changes.

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